tamine release, and the cells responsible for inflammation are able to migrate to the wound bed. The timeline for cell migration in a normal wound healing process is predictable.

[0018] Platelets, the first response cell, release multiple chemokines, including epidermal growth factor (EGF), fibronectin, fibrinogen, histamine, platelet-derived growth factor (PDGF), serotonin, and von Willebrand factor. These factors help stabilize the wound through clot formation. They act to control bleeding and limit the extent of injury. Platelet degranulation also activates the complement cascade, specifically C5a, which is a potent chemoattractant for neutrophils.

[0019] As the inflammatory phase continues, more immune response cells migrate to the wound. Neutrophil, the second response cell, is responsible for debris scavenging, complement-mediated opsonization of bacteria, and bacteria destruction via oxidative burst mechanisms (superoxide and hydrogen peroxide formation). The neutrophils kill bacteria and decontaminate the wound from foreign debris.

[0020] The next cells present in the wound are the leukocytes and the macrophages (monocytes). Macrophage is essential for wound healing. Numerous enzymes and cytokines are secreted by the macrophage, including collagenases, which debride the wound; interleukins and tumor necrosis factor (TNF), which stimulate fibroblasts (production of collagen) and promote angiogenesis; and transforming growth factor (TGF), which stimulates keratinocytes. This marks the transition into the process of tissue reconstruction, the proliferative phase.

[0021] Epithelialization, angiogenesis, granulation tissue formation, and collagen deposition are the principal steps in the proliferative phase of wound healing. Epithelialization occurs early in wound repair. If the basement membrane remains intact, the epithelial cells migrate upwards in the normal pattern, as in first-degree skin burn. The epithelial progenitor cells remain intact below the wound, and the normal layers of epidermis are restored in 2-3 days. If the basement membrane has been destroyed, similar to a second- or third-degree burn, then the wound is reepithelialized from the normal cells in the periphery and from the skin appendages, if intact (eg, hair follicles, sweat glands).

[0022] Angiogenesis, stimulated by TNF-alpha, is marked by endothelial cell migration and capillary formation. The new capillaries deliver nutrients to the wound and help maintain the granulation tissue bed. The migration of capillaries into the wound bed is critical for proper wound healing. The granulation phase and tissue deposition require nutrients supplied by the capillaries, and failure for this to occur results in a chronically unhealed wound. Mechanisms for modifying angiogenesis are under study and have significant potential to improve the healing process.

[0023] The final part of the proliferative phase is granulation tissue formation. Fibroblasts differentiate and produce ground substance and then collagen. The ground substance is deposited into the wound bed. Collagen is then deposited as the wound undergoes the final phase of repair. Many different cytokines are involved in the proliferative phase of wound repair. The steps and the exact mechanism of control have not been elucidated. Some of the cytokines include PDGF, insulin like growth factor (IGF), and EGF. All are necessary for collagen formation.

[0024] The final phase of wound healing is the maturational phase. The wound undergoes contraction, ultimately resulting in a smaller amount of apparent scar tissue. The entire wound healing process is a dynamic continuum with an overlap of each phase and continued remodeling. Wound reaches maximal strength at one year and result in a tensile strength that is 30% of normal skin. Collagen deposition continues for a prolonged period, but the net increase in collagen deposition plateaus after 21 days.

[0025] Proper wound healing involves a complex interaction of cells and cytokines working in concert. Particularly, cytokines and chemokines orchestrate the progression of healing and are fundamental to the cellular and biochemical events that occur during acute wound healing. These effectors can be measured in serum and wound effluent using modern molecular techniques.

[0026] Currently, the only available commercial product proven to be efficacious in wound healing is PDGF, which is available as recombinant human PDGF-BB. In multiple studies, recombinant human PDGF-BB has been demonstrated to reduce healing time and improve the incidence of complete wound healing in stage III and IV ulcers. Other cytokines being studied for wound healing include TGF-beta, EGF, and IGF-1.

[0027] Breast carcinoma is the most commonly diagnosed cancer and the second leading cause of cancer-related mortality among women in the United States [50]. In 2009, there were over 192,000 estimated new cases of cancer of the breast, and over 40,000 disease-specific deaths [50]. Breast cancer-related mortality rates have steadily decreased over the past two decades, largely due to improved disease detection and therapy [51].

[0028] As breast cancer in younger (under age 40) women is infrequently diagnosed in the early stages utilizing current screening guidelines, improved cancer screening and detection methods are important in current research, particularly in younger, at-risk women [52]. Breast cancer in younger women typically has unfavorable prognostic characteristics associated with increased disease-specific mortality [53-55]. Younger women are not typically referred for periodic imaging unless they are identified as being "high risk" [56]. "At risk" younger women with significant family history or genetic factors are encouraged to undergo frequent clinical and annual breast imaging surveillance, and to consider chemoprevention.

[0029] While increased surveillance for "at risk" women may be beneficial, the value of this approach is restricted by the rarity of breast cancer due to known genetic risk factors [57, 58]. Over 90% of breast cancers are detected in women who are not identified as "high risk" [52]. Furthermore, screening mammography is generally less accurate in younger women and those with increased breast tissue density commonly encountered in women under age 40 [59]. The reduced sensitivity of mammography for dense breasts impacts age groups in which a "life saved" often results in "higher" personal and societal costs in terms of altered life expectancy and personal productivity [60].

[0030] MRI is being used increasingly as a screening modality in high-risk women with a significant family history of breast cancer, or BRCA1 or BRCA2 gene mutations resulting in lifetime risk of cancer exceeding 20% [61]. Hence, breast MRI is applied to a relatively small proportion of all women. MRI is unaffected by breast tissue density; however, the high cost, requirement for intravenous contrast administration, and variable specificity limit its feasibility for widespread population-based screening [62, 63].